Remarks

Claim 1 has been amended. New claims 34-36 have been added. Claims 1-5, 7-9, 16, 30, and 33-36 are now in the application. Reconsideration and allowance of these claims as now presented is respectfully requested.

Rejection of Claims Under 35 U.S.C. §112

Claims 1-5, 7-9, 16, 30, and 33 stand rejected under 35 U.S.C. §112, first paragraph, as claiming subject matter not described in the specification. Specifically, the Examiner asserts that Applicant's specification does not provide support for the limitation "at least 80% of the chromone dissolves within 5 minutes". Applicant respectfully submits, however, that such claim language is in fact found at page 4 lines 11-15 as follows:

> "... preferably from ... 80% ... of the chromone dissolves within ... 5 ... minutes of subsequent exposure of the composition to simulated intestinal fluid."

While the Examiner is correct in stating that the specification at page 4 sets a lower limit on the amount of dissolution at 15%, the claim recitation of at least 80% chromone dissolution is within the spectrum defined by the lower limit of at least 15%. In addition, the Wigmore Declaration filed on December 9, 2002 further evidences the disclosure made at page 4 of Applicant's specification,

wherein at least about 80% of the chromone dissolves within about 5 minutes of subsequent exposure of the composition to simulated intestinal fluid. The claim rejections under 35 U.S.C. §112 should accordingly be withdrawn.

Rejection of Claims Under 35 U.S.C. §103

Claims 1-5, 7-9, 16, 30, and 33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Watts et al. (U.S. 6,200,602). The Watts et al. '602 is generally directed to a drug composition for delivery in the colon of the user. In particular, Watts et al. '602 disclose a composition that prevents release of the drug until the formulation reaches the colon (column 6 lines 21-24).

The Examiner asserts that since Watts et al. describe the optional use of known pharmaceutical excipients such as AVICEL™, that the composition of Watts et al. would have similar dissolution rates to that presently claimed. Applicant respectfully submits, however, that Watts et al. fail to teach or describe the rapid dissolution of the composition and rapid bioavailability of the polar drug as a goal or characteristic of its composition. In fact, column 6 of Watts et al. '602 describes the desire of allowing the capsule to breakup only after about 3-4 hours of exposure to intestinal fluid so that the composition will eventually be released in the colon.

The benefits of rapid dissolution, and thereby rapid bioavailability of the chromone of the present invention, are described at page 7 line 11-page 8 line 2 of the specification. Specifically, rapid dissolution of the compositions of the present invention has been found by the Applicant to have beneficial effects in treating allergic conditions relating to ingested substances. As such, the rapid dissolution characteristic of the present compositions is a core goal and advantage of the present invention over compositions of the prior art. Nowhere do Watts et al. '602 teach or suggest rapid composition dissolution in order to make the chromone bioavailable within the duodenum. Therefore, no motivation exists in the cited prior art to reach the presently claimed compositions.

Moreover, nowhere do Watts et al. '602 teach or suggest the presently claimed required ratio of disintegrant to chromone in order to achieve the above-described rapid composition dissolution. The Examiner states at page 4 of the Office Action dated October 31, 2003 that concentration differences over the prior art do not support patentability unless there is evidence indicating that such concentration difference is critical. Here, the relative concentrations of the disintegrant to

chromone in the compositions of the present invention are absolutely critical to the rapid dissolution characteristic, and therefore the successful performance of the claimed compositions. Such concentration criticality is described at page 17 lines 10-23 of the application as originally filed, as well as at page 3 line 3-page 4 line 13, and page 5 lines 8-11 of the Wigmore Declaration filed in Applicant's response of May 29, 2003. Applicant therefore submits that the claimed ratios present subject matter not taught or described in the cited prior art, and which provide the unique functional characteristics of the claimed compositions as described in the original application. The claim rejections based upon Watts et al. '602 should accordingly be withdrawn.

Claims 1-5, 7-9, 16, 30, and 33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wigmore (GB 2,324,962). Applicant respectfully points out to the Examiner that the Wigmore '962 patent was previously cited in an Office Action dated September 9, 2002. In response to such a citation, Applicant noted that the Wigmore '962 has a publication date of November 11, 1998. The effective filing date of the present application is the filing date of the British priority application no. 9824604.4, filed on November 11, 1998. A Supplemental Declaration evidencing

this priority claim is attached hereto. In light of the above, the Wigmore '962 patent is inoperative under 35 U.S.C. §102 as prior art against the present application.

Further attached hereto are experimental results utilizing compositions described in the application as originally filed. Such experimental results clearly establish and evidence the claimed dissolution rates using a variety of different disintegrant materials. Accordingly, Applicant respectfully submits that the disintegrant materials, as classified in the specification at pages 15-16, may be interchangeably utilized in the compositions of the present invention in order to obtain the claimed dissolution rates.

For the foregoing reasons, the claims as presently amended are believed to be unobvious and patentable over the cited prior art. Applicant therefore submits that the claims as currently presented are allowable on the merits. An early allowance is respectfully solicited.

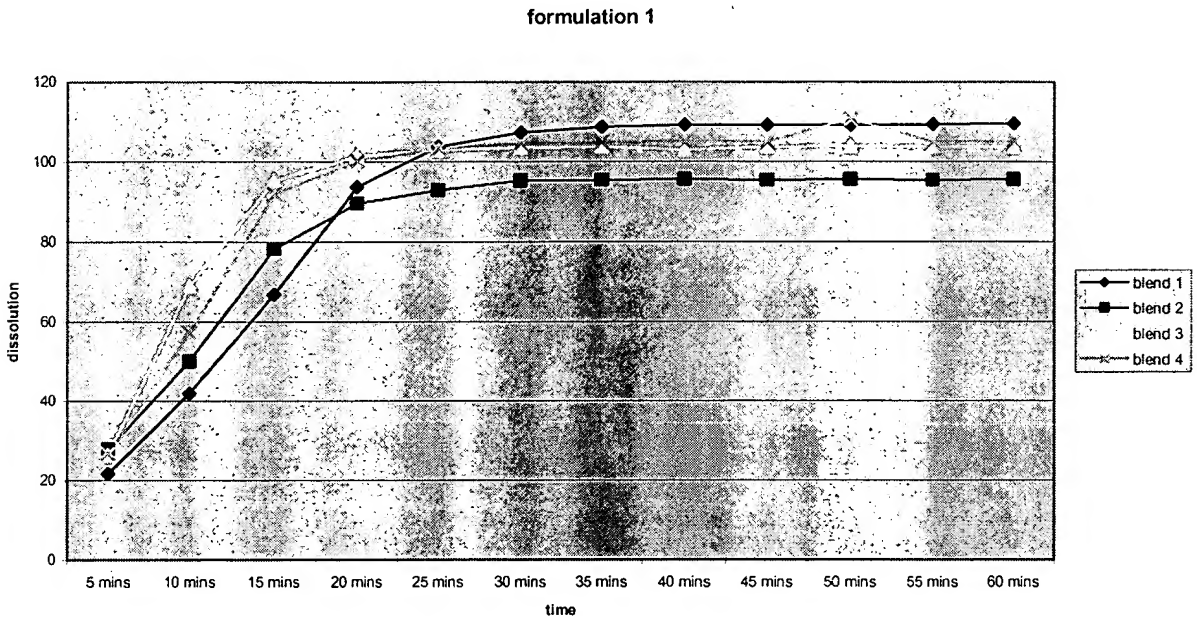
Respectfully submitted,

HAUGEN LAW FIRM PLLP

Mark J. Burns, Reg. #46591
Attorney for Applicant
1130 TCF Tower
121 South Eighth Street
Minneapolis, MN 55402
Phone: (612) 339-8300

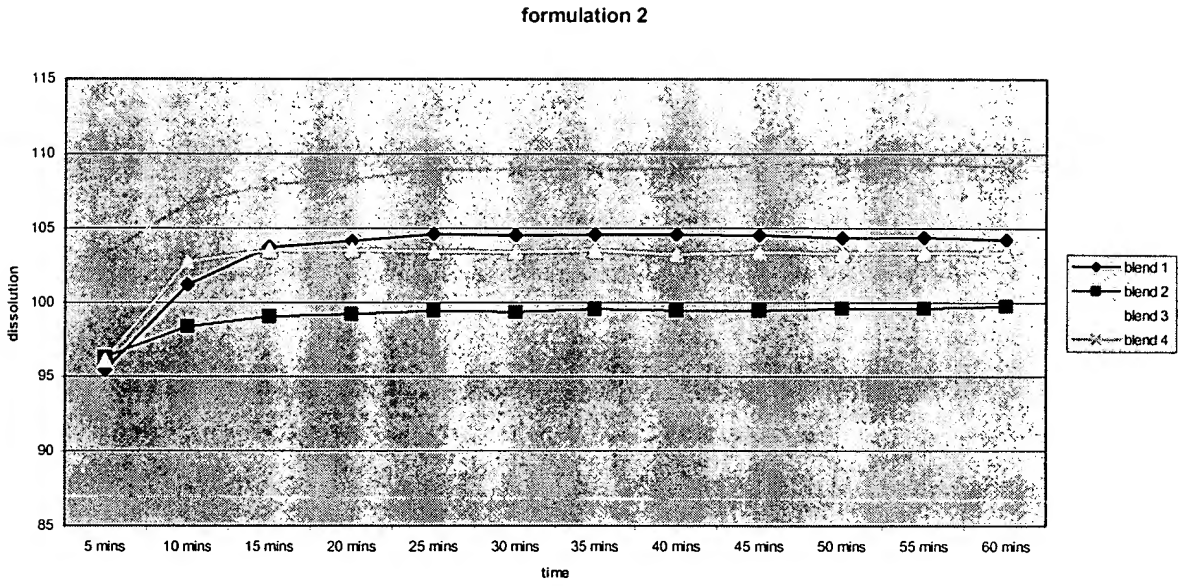
AVERAGE DISSOLUTION RESULTS FOR EACH FORMULATION

FORMULATION 1



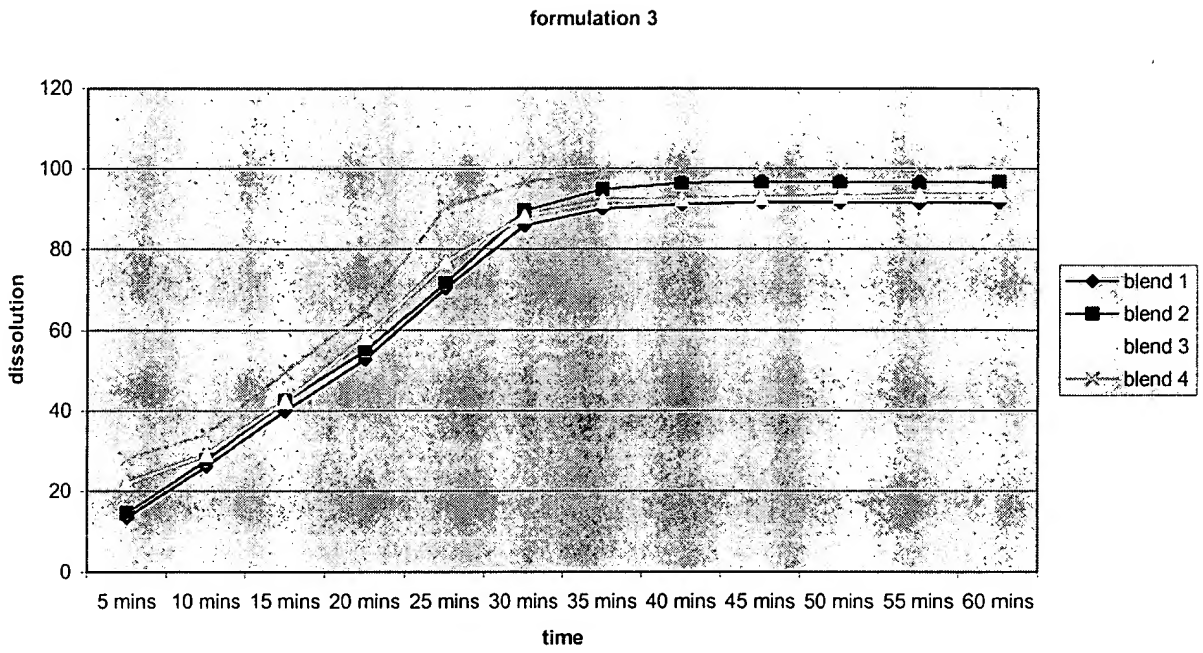
time	blend 1	blend 2	blend 3	blend 4
5 mins	21.71	27.93	26.43	26.72
10 mins	41.84	50.02	68.99	57.21
15 mins	66.87	78.3	95.21	91.98
20 mins	93.61	89.6	101.27	100.05
25 mins	103.64	92.87	102.87	103.21
30 mins	107.37	95.19	103.53	104.57
35 mins	108.63	95.3	103.61	104.74
40 mins	109.1	95.57	102.88	104.89
45 mins	109.2	95.39	103.67	104.98
50 mins	109.14	95.53	103.77	110.65
55 mins	109.29	95.44	103.62	104.87
60 mins	109.53	95.6	103.74	105.05

FORMULATION 2



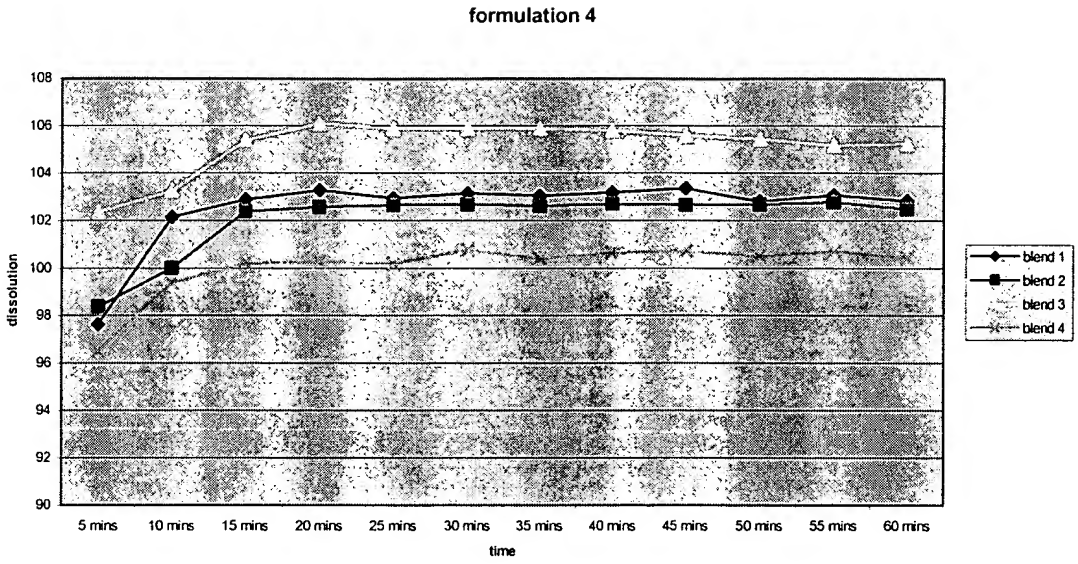
time	blend 1	blend 2	blend 3	blend 4
5 mins	95.43	96.3	96.1	103.21
10 mins	101.19	98.39	102.76	106.68
15 mins	103.72	99.04	103.53	107.92
20 mins	104.16	99.22	103.55	108.31
25 mins	104.62	99.42	103.45	108.99
30 mins	104.53	99.36	103.4	108.91
35 mins	104.57	99.55	103.53	108.93
40 mins	104.55	99.42	103.23	108.93
45 mins	104.54	99.45	103.35	109.31
50 mins	104.37	99.62	103.31	109.24
55 mins	104.41	99.6	103.34	109.31
60 mins	104.22	99.75	103.32	109.19

FORMULATION 3



time	blend 1	blend 2	blend 3	blend 4
5 mins	13.51	14.52	21.97	28.32
10 mins	26.29	27.75	29.19	34.22
15 mins	40.09	42.51	42.39	49.72
20 mins	52.77	54.93	58.17	64.93
25 mins	70.4	71.61	76.87	90.53
30 mins	85.89	89.61	88.1	96.72
35 mins	89.98	94.83	91.95	99.17
40 mins	91.19	96.44	92.36	99.56
45 mins	91.53	96.69	92.72	99.7
50 mins	91.53	96.75	92.92	99.59
55 mins	91.48	96.62	93.32	99.3
60 mins	91.56	96.68	93.41	101.235

FORMULATION 4



time	blend 1	blend 2	blend 3	blend 4
5 mins	97.63	98.38	102.35	96.53
10 mins	102.16	100.02	103.26	99.42
15 mins	102.89	102.39	105.38	100.23
20 mins	103.29	102.56	106.11	100.28
25 mins	102.95	102.64	105.89	100.2
30 mins	103.15	102.68	105.88	100.79
35 mins	103.04	102.62	105.89	100.42
40 mins	103.18	102.71	105.82	100.66
45 mins	103.36	102.64	105.61	100.73
50 mins	102.8	102.68	105.44	100.51
55 mins	103.08	102.79	105.18	100.72
60 mins	102.84	102.5	105.26	100.44

Sodium Cromoglycate Tablet Development & Dissolution Study

Background: A tablet formulation had previously been developed for the oral delivery of SCG. During the development of the tablet formulation, a study had been performed to identify the optimum SCG:MCC ratio for rapid tablet dissolution. Four tablet blends had been produced with varying SCG:MCC ratios and the dissolution profiles of each recorded.

Current Study Objective: To investigate the effects of replacing MCC with various other disintegrants.

Process: Four batches of granules were prepared, each containing a different disintegrant as follows:

Formulation 1	- Croscarmellose Sodium
Formulation 2	- Crospovidone
Formulation 3	- Sodium Starch Glycolate
Formulation 4	- Croscarmellose Na : MCC (1:9)

Each batch of granules was then divided into four sub-batches and blended with varying amounts of disintegrant (to match the SCG:MCC ratios of the original study). The sub-batches (blends) were then compressed into tablets using the rotary tablet press and dissolution tested in the laboratory so that their release profiles could be compared.

The SCG : Disintegrant ratios for each formulation were as follows:

Blend 1	1 : 1
Blend 2	1 : 1.2
Blend 3	1 : 1.4
Blend 4	1 : 1.6

Three tablets from each blend were dissolution tested in phosphate buffer. Samples of dissolution media were taken every 5 minutes over a 60 minute test period. The mean percentage dissolution was calculated for each blend at each timepoint and plotted for comparison (Appendix 1). The results were expressed as percentages of the theoretical SCG dose (calculated according to formulation and actual tablet weight).

Discussion:

Formulation 1 (Croscarmellose Sodium): The tablets from all four blends had reached their maximum dissolution at approximately 25 - 30 minutes. At 15 minutes, however, there was a marked difference between the performance of the Blends. Those with less disintegrant (1 & 2) had released significantly less SCG than those with more (3 & 4). The release

profiles of Blends 3 and 4, however, were very similar, suggesting the optimum SCG : Disintegrant ratio is approximately 1 : 1.4.

Formulation 2 (Crospovidone): The tablets from all four blends dissolved very rapidly. Each Blend achieved greater than 95% dissolution within 5 minutes. If the results were normalised so the maximum dissolution value achieved is taken as 100%, Blend 2 would be seen to dissolve quicker than the others initially, suggesting an optimum SCG : Disintegrant ratio of 1 : 1.2.

Formulation 3 (Sodium Starch Glycolate): The tablets from all four blends were slow to dissolve relative to the batches made with other disintegrants. This would suggest that sodium starch glycolate is least suitable for use as the disintegrant in the SCG tablet formulation.

Formulation 4 (Croscarmellose Sodium : MCC (1 : 9)): These tablet formulations (of the four included in this study) were the closest to the MCC-containing formulations in the original work. The variation was the addition of Croscarmellose Sodium at a ration of 1:9 to the MCC. The resulting tablets disintegrated very rapidly, but if the results were normalised to 100% Blend 3 would demonstrate the most rapid initial rate of dissolution. This result mirrored the observations made in the original and would suggest an optimum SCG : Disintegrant ratio of 1 : 1.4.

Appendices: Appendix 1 - Dissolution Data

SODIUM CROMOGLYCOLATE TABLET DEVELOPMENT AND DISSOLUTION STUDY

Four Tablet formulations used to produce 4 blends each - TOTAL = 16 Blends

DISSOLUTION PROFILES (60 minutes)

Formulation 1 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	19.62	23.24	22.26	21.71
10 mins	39.95	42.46	43.12	41.84
15 mins	61.61	67.98	71.03	66.87
20 mins	92.71	93.84	94.27	93.61
25 mins	103.29	102.49	105.13	103.64
30 mins	107.25	105.51	109.35	107.37
35 mins	108.12	106.8	110.97	108.63
40 mins	108.35	107.61	111.33	109.1
45 mins	108.39	107.46	111.76	109.2
50 mins	108.63	107.5	111.3	109.14
55 mins	108.53	107.61	111.74	109.29
60 mins	108.94	107.94	111.72	109.53

Formulation 1 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	29.51	27.2	27.08	27.93
10 mins	50.51	52.63	46.93	50.02
15 mins	80.07	78.84	75.99	78.3
20 mins	89.11	89.04	90.65	89.6
25 mins	92.13	91.91	94.58	92.87
30 mins	94.29	94.04	97.23	95.19
35 mins	94.29	94.15	97.45	95.3
40 mins	94.26	94.47	97.97	95.57
45 mins	94.35	94.19	97.64	95.39
50 mins	94.61	94.19	97.79	95.53
55 mins	94.3	94.32	97.71	95.44
60 mins	94.39	94.4	98.01	95.6

Formulation 1 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	26.75	24.64	27.91	26.43
10 mins	78.87	62.65	65.45	68.99
15 mins	89.24	97.38	99.01	95.21
20 mins	92.57	102.48	108.76	101.27
25 mins	93.08	104.48	111.05	102.87
30 mins	93.33	105.19	112.07	103.53
35 mins	93.44	105.14	112.26	103.61
40 mins	93.45	105.26	109.92	102.88
45 mins	93.35	105.4	112.25	103.67
50 mins	93.5	105.41	112.39	103.77
55 mins	93.52	104.98	112.37	103.62
60 mins	93.58	105.18	112.46	103.74

Formulation 1 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	26.661	25.799	27.689	26.72
10 mins	53.784	57.822	60.031	57.21
15 mins	93.567	96.829	83.963	91.98
20 mins	100.524	101.962	97.653	100.05
25 mins	102.461	103.522	103.641	103.21
30 mins	103.491	104.218	106	104.57
35 mins	103.569	104.202	106.459	104.74
40 mins	103.935	104.277	106.454	104.89
45 mins	103.837	104.595	106.506	104.98
50 mins	120.779	104.442	106.733	110.65
55 mins	103.763	104.35	106.492	104.87
60 mins	103.712	104.258	107.183	105.05

Formulation 2 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	93.973	94.385	97.944	95.43
10 mins	100.802	100.836	101.946	101.19
15 mins	103.025	104.278	103.851	103.72
20 mins	103.249	104.924	104.319	104.16
25 mins	104.065	105.38	104.399	104.62
30 mins	104.049	105.325	104.239	104.53
35 mins	103.964	105.321	104.474	104.57
40 mins	103.969	105.428	104.257	104.55
45 mins	104.033	105.562	104.026	104.54
50 mins	103.666	105.289	104.14	104.37
55 mins	103.818	105.065	104.352	104.41
60 mins	103.63	105.179	103.837	104.22

Formulation 2 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	94.923	98.831	95.146	96.3
10 mins	96.804	100.758	97.614	98.39
15 mins	97.91	100.911	98.309	99.04
20 mins	97.573	101.277	98.806	99.22
25 mins	97.424	101.267	99.198	99.42
30 mins	97.687	101.385	99.018	99.36
35 mins	97.985	101.564	99.097	99.55
40 mins	97.538	101.497	99.237	99.42
45 mins	97.623	101.72	99.017	99.45
50 mins	98.05	101.619	99.184	99.62
55 mins	97.687	101.722	99.38	99.6
60 mins	97.983	101.563	99.687	99.75

Formulation 2 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	97.55	98.711	92.029	96.1
10 mins	102.47	102.791	103.033	102.76
15 mins	103.007	103.497	104.092	103.53
20 mins	103.072	103.624	103.942	103.55
25 mins	102.74	103.499	104.114	103.45
30 mins	102.92	103.375	103.894	103.4
35 mins	103.043	103.53	104.03	103.53
40 mins	102.836	103.168	103.698	103.23
45 mins	102.749	103.491	103.815	103.35
50 mins	102.98	103.296	103.654	103.31
55 mins	102.886	103.296	103.826	103.34
60 mins	102.687	103.515	103.754	103.32

Formulation 2 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	101.137	101.893	106.589	103.21
10 mins	107.119	106.983	105.924	106.68
15 mins	108.972	108.622	106.177	107.92
20 mins	109.708	109.057	106.159	108.31
25 mins	110.448	109.678	106.877	108.99
30 mins	110.33	109.546	106.844	108.91
35 mins	110.243	109.498	107.054	108.93
40 mins	110.322	109.67	106.796	108.93
45 mins	110.595	109.929	107.395	109.31
50 mins	110.416	110.178	107.135	109.24
55 mins	110.95	109.912	107.066	109.31
60 mins	110.514	109.909	107.142	109.19

Formulation 3 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	14.723	13.005	12.809	13.51
10 mins	27.436	25.241	26.19	26.29
15 mins	40.544	39.241	40.482	40.09
20 mins	52.543	52.003	53.778	52.77
25 mins	74.935	64.043	72.217	70.4
30 mins	82.997	87.892	86.77	85.89
35 mins	85.283	93.045	91.626	89.98
40 mins	85.75	94.659	93.164	91.19
45 mins	85.969	95.04	93.59	91.53
50 mins	86.098	94.991	93.499	91.53
55 mins	85.785	95.037	93.611	91.48
60 mins	86.117	95.076	93.477	91.56

Formulation 3 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	15.727	14.685	13.153	14.52
10 mins	29.844	28.56	24.846	27.75
15 mins	45.383	45.079	37.074	42.51
20 mins	58.437	58.348	48.012	54.93
25 mins	84.183	72.391	58.249	71.61
30 mins	92.421	93.551	82.866	89.61
35 mins	94.067	99.277	91.16	94.83
40 mins	94.992	100.669	93.661	96.44
45 mins	94.611	101.152	94.292	96.69
50 mins	94.735	100.772	94.728	96.75
55 mins	94.61	100.912	94.335	96.62
60 mins	94.54	100.782	94.708	96.68

Formulation 3 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	21.389	21.069	23.464	21.97
10 mins	29.02	27.295	31.246	29.19
15 mins	42.048	40.732	44.392	42.39
20 mins	60.713	54.234	59.564	77.33
25 mins	71.087	78.519	81.008	76.87
30 mins	91.611	84.935	87.754	88.1
35 mins	98.693	87.188	89.976	91.95
40 mins	98.451	88.013	90.601	92.36
45 mins	98.811	88.376	90.96	92.72
50 mins	99.282	88.504	90.982	92.92
55 mins	99.639	88.942	91.381	93.32
60 mins	99.451	89.025	91.742	93.41

Formulation 3 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	29.087	29.668	26.195	28.32
10 mins	33.751	34.982	33.931	34.22
15 mins	48.482	50.128	50.539	49.72
20 mins	63.326	65.963	65.49	64.93
25 mins	90.564	91.015	89.996	90.53
30 mins	96.456	96.211	97.497	96.72
35 mins	98.919	99.034	99.569	99.17
40 mins	98.818	99.946	99.927	99.56
45 mins	99.273	99.878	99.939	99.7
50 mins	98.76	99.992	100.019	99.59
55 mins	99.606	98.762	99.529	99.3
60 mins	99.051	100.16	101.235	100.15

Formulation 4 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.832	97.413	95.652	97.63
10 mins	102.841	103.899	99.738	102.16
15 mins	103.244	104.676	100.761	102.89
20 mins	103.674	105.057	101.147	103.29
25 mins	103.35	104.975	100.523	102.95
30 mins	103.535	105.011	100.895	103.15
35 mins	103.385	104.92	100.821	103.04
40 mins	103.62	104.942	100.979	103.18
45 mins	103.035	104.925	100.564	103.36
50 mins	103.24	104.785	100.375	102.8
55 mins	103.407	105.157	100.681	103.08
60 mins	103.331	104.819	100.383	102.84

Formulation 4 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.112	93.724	102.317	98.38
10 mins	101.597	92.171	106.278	100.02
15 mins	102.476	98.323	106.381	102.39
20 mins	102.55	98.538	106.582	102.56
25 mins	102.635	98.369	106.921	102.64
30 mins	102.642	98.487	106.903	102.68
35 mins	102.611	98.355	106.906	102.62
40 mins	102.77	98.347	107.279	102.71
45 mins	102.509	98.414	106.582	102.64
50 mins	102.841	98.341	106.845	102.68
55 mins	102.956	98.395	107.018	102.79
60 mins	102.415	98.437	106.642	102.5

Formulation 4 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.844	105.363	101.856	102.35
10 mins	103.867	108.279	103.261	103.26
15 mins	104.721	108.467	102.95	105.38
20 mins	104.963	108.684	104.696	106.11
25 mins	104.86	108.648	104.15	105.89
30 mins	104.586	108.814	104.233	105.88
35 mins	104.629	109.042	104.004	105.89
40 mins	105.021	108.541	103.906	105.82
45 mins	104.581	108.573	103.679	105.61
50 mins	104.449	108.246	103.614	105.44
55 mins	104.132	107.929	103.478	105.18
60 mins	103.923	108.193	103.667	105.26

Formulation 4 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	98.457	93.7	97.422	96.53
10 mins	101.358	96.505	100.407	99.42
15 mins	101.783	97.487	101.424	100.23
20 mins	101.85	97.504	101.642	100.28
25 mins	102.01	97.13	101.457	100.2
30 mins	102.565	97.764	102.03	100.79
35 mins	102.029	97.595	101.634	100.42
40 mins	102.267	97.687	102.03	100.66
45 mins	102.47	97.801	101.927	100.73
50 mins	102.067	97.686	101.771	100.51
55 mins	102.429	97.524	102.192	100.72
60 mins	102.395	97.368	101.569	100.44